EXHIBIT A139

Research Article

Cancer Prevention Research

Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls

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Abstract

Genital powder use has been associated with risk of epithelial ovarian cancer in some, but not all, epidemiologic investigations, possibly reflecting the carcinogenic effects of talc particles found in most of these products. Whether risk increases with number of genital powder applications and for all histologic types of ovarian cancer also remains uncertain. Therefore, we estimated the association between self reported genital powder use and epithelial ovarian cancer risk in eight population based case control studies. Individual data from each study were collected and harmonized. Lifetime number of genital powder applications was estimated from duration and frequency of use. Pooled ORs were calculated using conditional logistic regression matched on study and age and adjusted for potential confounders. Subtype specific risks were estimated according to tumor behavior and histology. 8,525 cases and 9,859 controls were included in the analyses. Genital powder use was associated with a modest increased risk of epithelial ovarian cancer [OR, 1.24; 95% confidence interval (CI), 1.15 1.33] relative to women who never used powder. Risk was elevated for invasive serous (OR, 1.20; 95% CI, 1.09 1.32), endometrioid (OR, 1.22; 95% CI, 1.04 1.43), and clear cell (OR, 1.24; 95% CI, 1.01 1.52) tumors, and for borderline serous tumors (OR, 1.46; 95% CI, 1.24 1.72). Among genital powder users, we observed no significant trend ($P = 0.17$) in risk with increasing number of lifetime applications (assessed in quartiles). We noted no increase in risk among women who only reported nongenital powder use. In summary, genital powder use is a modifiable exposure associated with small to moderate increases in risk of most histologic subtypes of epithelial ovarian cancer. *Cancer Prev Res; 6(8); 811 21. ©2013 AACR.*

Introduction

Powders that are commonly applied either directly to the genital, perineal, or rectal area after bathing or indirectly to underwear, sanitary napkins, tampons, or stored contracep tive devices may contain talc because of its softness, absor bency, and lack of clumpiness (1). However, the presence of talc in commercially available powder formulations has varied over time, even within particular brands of products, limiting the ability of most epidemiologic studies to mea sure genital talc exposure accurately. Despite this, genital powder use, but not use on other parts of the body, has been linked to increased risk of ovarian cancer, suggesting that powder particles ascending the genital tract may predispose to ovarian cancer development (2 4). Meta analyses of

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observational studies show 33% to 35% increased risk of ovarian cancer among women who have used genital pow ders (1, 4, 5), but evidence for a dose response relationship has been inconsistent. Although dose response was not addressed in previous meta analyses (1, 4, 5), some indi vidual studies have reported significant dose response (4, 6 10) while others have not (9, 11 15).

Epidemiologic and biologic studies show differences in risk factor profiles and molecular characteristics between ovarian cancer subtypes defined by histology (serous, endo metrioid, mucinous, and clear cell) and behavior (border line and invasive; refs. 16 and 17). For instance, serous tumors are characterized by p53 mutations, whereas mucin ous tumors have a high prevalence of KRAS mutations (17) and are not generally associated with reproductive risk factors (16, 18). Because most early studies of powder use and ovarian cancer did not include analysis by histologic subgroups (3, 6, 11, 19 21), histology specific estimates were not available from these studies for meta analysis. Most (2, 4, 8, 9, 22), but not all (10, 14, 15, 23), epidemi ologic studies of genital powder use and risk of ovarian cancer that have evaluated histologic subgroups have found the association to be strongest for serous invasive tumors. Such tumors comprise the most common variety of ovarian cancer and few previous studies have had sufficient statis tical power to evaluate the association between genital powder use and risk of other histologic subtypes. In the present study, we evaluated associations between genital powder use and risk of ovarian cancer overall, by invasive ness and by histologic type in a pooled analysis of eight population based case control studies with relevant data from the Ovarian Cancer Association Consortium (OCAC), a consortium founded in 2005 to validate promising genetic associations in epidemiologic studies of ovarian cancer.

Materials and Methods

Participating studies

Studies participating in the OCAC consortium as of April 2010 that collected data on powder use were included. Each study was approved by an institutional ethics committee and all participants provided informed consent. Detailed description of the OCAC consortium is available elsewhere (24). Characteristics of the eight case control studies con tributing data to this analysis are presented in Table 1. Six studies were conducted in the United States [Diseases of the Ovary and their Evaluation Study (DOV; ref. 14), Hawaii Ovarian Cancer Study (HAW; ref. 25), Hormones and Ovarian Cancer Prediction Study (HOP; ref. 26), North Carolina Ovarian Cancer Study (NCO; ref. 27), New Eng land Case Control Study of Ovarian Cancer (NEC; ref. 4), and University of Southern California Study of Lifestyle and Women's Health (USC; ref. 28)], one study in Australia [Australian Cancer Study (AUS; ref. 7)], and one study in Canada [Southern Ontario Ovarian Cancer Study (SON; ref. 15)]. Overall, our analyses included 8,525 cases of ovarian, fallopian tube, or peritoneal cancer and 9,859 controls. Five studies previously reported on powder use [AUS (7), DOV (14), NCO (27), NEC (4), and SON (15)], three of which provided data for this analysis that had not been included in their previous powder related publication (DOV, NEC, and AUS). The remaining three studies have not previously published their genital powder use data (HAW, HOP, and USC).

Exposure and covariate data

Data collected from participants about genital powder use varied between studies. Harmonized analytic exposure variables were developed by comparing questionnaires between the eight participating studies. The majority of the studies have obtained information on duration and fre quency of powder use, age at first powder use, use by sexual partners, and non genital use (Table 1). We defined genital powder use as any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area. Because study specific powder questions included varying degrees of detail about type and method of application, genital pow der definitions differ between studies. Criteria for regular genital powder use varied between studies from "ever use" (AUS) to "one year or longer" (DOV); the specific wording for this question is provided in Table 1. Use of body powders on sites other than the genital area was defined as non genital powder use. Women who reported both genital and non genital powder use were classified as genital users. Two studies (DOV and SON) did not collect data on nongenital use, and therefore women assigned to "no powder use" for these studies could have a history of non genital powder exposure. Extensive information on known and suspected risk factors for ovarian cancer was collected in each study, including oral contraceptive use, parity, tubal ligation history, body mass index (BMI), race, and ethnicity.

Statistical analysis

Participants missing case/control status ($n = 17$) or tumor histology ($n = 19$) were excluded from the analysis. We also excluded 1,119 participants who answered "do not know" or were missing data on genital powder use; most of these were from the NCO study, which did not include genital powder questions for the first 720 participants. Furthermore, we excluded participants missing tubal liga tion ($n = 55$), oral contraceptive duration ($n = 100$), parity ($n = 3$), or height or weight (BMI; $n = 179$). To examine differences in characteristics between cases and controls, we evaluated two sample t statistics (age and BMI) and χ^2 statistics (oral contraceptive use, nulliparity, tubal ligation, race/ethnicity, and powder use).

Study specific ORs and 95% confidence intervals (CI) were estimated using unconditional logistic regression and were summarized by forest plots, including study hetero geneity based on Cochran's Q statistic. As no significant heterogeneity was observed between studies, we calculated pooled ORs and 95% CIs across the studies using condi tional logistic regression matched on 5 year age groups and

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Table 1. Characteristics of eight studies included in the analysis of genital powder use and ovarian cancer

Study[a]	Diagnosis years	Controls	Cases	Histology[b]				Behavior[c]		Question used to define genital powder use
				Serous	Mucinous	Endometrioid	Clear cell	Invasive	Borderline	
AUS[9]	2002–2006	1 449	1 432	889 (62%)	174 (12%)	132 (9%)	78 (5%)	1 158 (81%)	274 (19%)	Have you ever used any sort of powder or talc on your genital area in your underwear or on a sanitary pad or diaphragm?
DOV[9]	2002–2009	1 841	1 565	905 (58%)	186 (12%)	201 (13%)	87 (6%)	1 153 (74%)	412 (26%)	Before (reference date) did you ever use any of the following products routinely during 1 month or more? Powder on sanitary napkins or pads? Vaginal deodorant spray? Before (reference date) did you usually apply any powder to your genital (perineal) area after bathing? We are only interested in times when you did this for at least 1 year or longer [d]
HAW	1993–2008	755	481	222 (46%)	87 (18%)	69 (14%)	47 (10%)	392 (82%)	89 (19%)	Before (month/year of diagnosis[e]) did you ever use talc baby or deodorizing powder dusted or sprayed on your body? By regularly mean at least once a month for 6 months or more Did you ever use talc baby or deodorizing powder as a dusting powder to the genital or rectal area? As a dusting powder to sanitary napkins? As a dusting powder to underwear? On a diaphragm or cervical cap?
HOP	2003–2008	1 489	735	433 (59%)	53 (7%)	75 (10%)	47 (6%)	568 (88%)	80 (12%)	As an adult and before (reference month/year) did you ever use talc or baby powder or deodorizing powder with talc at least once a month for 6 months or more in any of the following ways as a dusting powder or deodorizing spray to your genital or rectal areas? On your sanitary napkin? On your underwear? On your diaphragm or cervical cap?
NCO[9]	1999–2008	650	786	489 (62%)	71 (9%)	100 (13%)	65 (8%)	636 (81%)	148 (19%)	Did you ever regularly use cornstarch talc baby or deodorizing powders (dusted or sprayed) at least 1 time per month for at least 6 months? f yes please tell me if you used cornstarch talc baby or deodorizing powders in any of the following ways directly to your genital or rectal areas? Applied to your sanitary napkins or tampons? Applied to birth control devices such as cervical cap or diaphragm? Applied to your underwear?

(Continued on the following page)

Table 1. Characteristics of eight studies included in the analysis of genital powder use and ovarian cancer (Cont'd)

Study[a]	Diagnosis years	Controls	Cases	Histology[b]				Behavior[c]		Question used to define genital powder use
				Serous	Mucinous	Endometrioid	Clear cell	Invasive	Borderline	
NEC[g]	1992–2008	2 329	2 305	1 234 (54%)	281 (12%)	352 (15%)	276 (12%)	1 659 (77%)	486 (23%)	Did you ever regularly use powder on your body or your underwear (at least once per month for any amount of time)? f yes did you apply powder directly to your genital or rectal areas? To your sanitary napkins or tampons? To your underwear?[f]
SON[g]	1989–1992	564	449	254 (57%)	80 (18%)	71 (16%)	29 (6%)	365 (81%)	84 (19%)	Have you ever used sanitary napkins/tampons? f yes could you tell me over what ages you have used them for how many years what percentage of periods you have used them for the usual number you have used for each period whether they were deodorant pads/ tampons and if you used talcum powder or starch on them? Have you ever regularly used talcum powder or starch on your vaginal area after showering or bathing?
USC	1993–1997	782	772	396 (52%)	131 (17%)	75 (10%)	32 (4%)	549 (73%)	205 (27%)	Before (reference month/year) did you ever regularly use talc baby or deodorizing powder dusted or sprayed on your body? By regularly mean at least once a month for 6 months or more Did you ever use talc baby or deodorizing powder as a dusting powder to the genital or rectal area? As a dusting powder to sanitary napkins? As a dusting powder to underwear? On a diaphragm or cervical cap?

[a]AUS, Austra an Cancer Study; DOV, D seases of the Ovary and the r Eva uat on Study; HAW, Hawa Ovar an Cancer Study; HOP, Hormones and Ovar an Cancer Pred ct on Study; NCO, North Caro na Ovar an Cancer Study; NEC, New Eng and Case Contro Study; SON, Southern Ontar o Ovar an Cancer Study; and USC, Un vers ty of Southern Ca forn a Study of L festy e and Women s Hea th.

[b]Cases sted by h sto ogy do not sum because m xed, other, und fferent ated, and unknown are not nc uded.

[c]Cases sted by behav or do not sum to the tota number of cases because 267 cases are m ss ng behav or nformat on.

[d]n a separate ser es of quest ons, part c pants were asked about powder use w th d aphragm storage. Durat on was ca cu ated from ages of use. nformat on on durat on, frequency, and t m ng of use was on y co ected on gen ta /per na powder use after bath ng.

[e]Contro s were asked "Have you ever regu ar y used. . ."

[f]NEC quest on var ed s ght y between the three study phases. Between 1992 and 1997 part c pants were asked, "As an adu t and before (reference month/year), d d you regu ar y use ta c, baby, or deodor z ng powders dusted or sprayed to your body n any of the fo ow ng ways:". Between 1998 and 2003, women were asked "D d you regu ar y app y cornstarch, ta c, baby, or deodor z ng body powder at east one t me per month for 6 months or onger? f yes, p ease te me f you regu ar y app ed cornstarch, ta c, baby or deodor z ng body powders n any of the fo ow ng ways:" Between 2003 and 2008 part c pants were asked the quest on sted above.

[g]These stud es prev ous y pub shed on gen ta powder use and ovar an cancer r sk. AUS, DOV, and NEC prov ded new data to the poo ed ana yses presented here that were not nc uded n prev ous pub cat ons.

study. All analyses were adjusted for potential confounders: age (continuous), duration of oral contraceptive use (never use, use <2, 2 <5, 5 <10, or ≥10 years), parity (0, 1, 2, 3, or ≥4 children), tubal ligation history, BMI (quartiles based on distribution in controls), and race/ethnicity (non His panic White, Hispanic White, Black, Asian, or other). Family history of breast or ovarian cancer was also considered as covariate but was not included in the final model.

Subtype specific estimates were calculated for subgroups of ovarian cancer defined by behavior (invasive and bor derline) and histology (serous, mucinous, endometrioid, and clear cell) by comparing each case group with all controls. As borderline endometrioid and clear cell tumors are rare, we did not have sufficient numbers to evaluate those types separately.

To measure cumulative dose of genital powder use, we estimated lifetime number of powder applications by mul tiplying total months of use by frequency of use per month, for all direct and indirect genital powder applications. Women who reported multiple types of genital powder exposure (on underwear, on sanitary napkins or pads, or directly to genital area) during the same time period were assigned the number of genital powder applications equal to the most commonly used type rather than the sum of applications across all types of genital powder exposure. We reasoned that contemporaneous powder applications were unlikely to be independent events and therefore should not be treated cumulatively. Analyses of estimated lifetime number of applications excluded participants in the HOP study as data on age and frequency of use were not collected ($n = 2,224$); genital powder users' missing information on duration or frequency of use were omitted in the remaining studies ($n = 394$). Never regular users of genital powders and women who only reported nongenital use were coded as having zero lifetime genital powder applications and comprised the reference group for this analysis. Categories were determined on the basis of age specific quartile cutoff points in controls (25th, 50th, and 75th percentile cutoff points are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41 50 years; 720, 3,600, and 10,800 for 51 60 years; 1,440, 5,760, and 14,440 for 61 70; 840, 7,200, and 18,000 for > 70 years). Trends were evaluated on the basis of the median lifetime number of genital powder applications for controls in each age specific quartile using the Wald statistic and were conducted both including and excluding never users of genital powders.

We estimated the association between genital powder use and ovarian cancer risk within strata to evaluate poten tial modification of effect defined using a cutoff point BMI of 30 based on the World Health Organization's definition of obesity, endometriosis, parity, tubal ligation/hysterec tomy, and menopausal status. We used likelihood ratio statistics comparing models with and without interaction terms to determine statistically significant interactions. To estimate calendar year of first use, we subtracted the years since first use (age at study entry minus age at first genital powder use) from median calendar year of the participant's study.

All analyses were conducted in SAS v9.2 (SAS) and Stata v9.2 (StataCorp). All *P* values are two sided. Analyses have been independently verified by two separate study groups (HAW and NCO).

Results

This pooled analysis of eight case control studies includ ed 9,859 controls and 8,525 ovarian cancer cases. Genital powder use was reported by 2,511 (25%) of the controls and 2,600 (31%) of the cases, whereas powder use only on other (nongenital) parts of the body was reported by 1,533 (16%) of the controls and 1,282 (15%) of the cases (Table 2). The prevalence of genital powder use in controls varied widely between study sites, highest in AUS (45%) and lowest in HAW (15%; Table 3).

In the pooled analysis, ever regular use of genital powder was associated with a modest increase in risk of ovarian cancer (OR, 1.24; 95% CI, 1.15 1.33; Table 3) relative to women who reported no powder use (AUS, HAW, HOP,

Table 2. Characteristics of cases and controls included in the pooled analysis[a]

	Controls (*N* 9,859) Mean (STD) or *N* (%)	Cases (*N* 8,525) Mean (STD) or *N* (%)
Age	55 (12)	55 (12)
Oral contraceptive use		
Never	2,995 (30)	3,411 (40)
Ever	6,864 (70)	5,114 (60)
Parous		
No	1,468 (15)	2,196 (26)
Yes	8,391 (85)	6,329 (74)
Tubal ligation		
No	7,359 (75)	6,994 (82)
Yes	2,500 (25)	1,531 (18)
BMI	26.5 (6.1)	27.0 (6.6)
Race/ethnicity		
Non-Hispanic White	8,629 (88)	7,433 (87)
Hispanic White	197 (2)	214 (3)
Black	273 (3)	268 (3)
Asian	350 (4)	313 (4)
Other[b]	407 (4)	291 (4)
Powder use[c]		
Never use	5,815 (59)	4,643 (54)
Non-genital use only	1,533 (16)	1,282 (15)
Genital use	2,511 (25)	2,600 (31)

[a]All characteristics listed except age differed significantly (<0.01) between cases and controls. Cases include both borderline and invasive ovarian cancers.
[b]There are 6 cases and 3 controls missing race/ethnicity information.
[c]Categories for non-genital and genital powder use are mutually exclusive.

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Table 3. Association between powder use and risk of ovarian cancer (borderline and invasive combined) by study site

Site	Controls (%) (*N* 9,859)	Cases (%) (*N* 8,525)	Age-adjusted OR (95% CI)[a]	Multivariate OR (95% CI)[a]
AUS				
No powder use	305 (21)	300 (21)	1.00	1.00
Non-genital use only	486 (34)	427 (30)	0.85 (0.69–1.05)	0.92 (0.74–1.14)
Genital use	658 (45)	705 (49)	1.04 (0.85–1.26)	1.13 (0.92–1.38)
DOV[b]				
No powder use	1,544 (83)	1,293 (83)	1.00	1.00
Genital use	297 (16)	272 (17)	1.14 (0.95–1.37)	1.13 (0.93–1.36)
HAW				
No powder use	489 (65)	326 (68)	1.00	1.00
Non-genital use only	154 (20)	81 (17)	0.79 (0.58–1.07)	0.69 (0.50–0.96)
Genital use	112 (15)	74 (15)	0.99 (0.72–1.37)	0.99 (0.70–1.41)
HOP				
No powder use	989 (66)	439 (60)	1.00	1.00
Non-genital use only	184 (13)	102 (14)	1.23 (0.94–1.61)	1.23 (0.93–1.62)
Genital use	316 (21)	194 (26)	1.37 (1.11–1.69)	1.34 (1.07–1.67)
NCO				
No powder use	391 (60)	469 (60)	1.00	1.00
Non-genital use only	137 (21)	122 (16)	0.75 (0.57–0.99)	0.74 (0.56–0.99)
Genital use	122 (19)	195 (25)	1.33 (1.03–1.74)	1.37 (1.05–1.80)
NEC				
No powder use	1,239 (53)	1,129 (49)	1.00	1.00
Non-genital use only	454 (19)	421 (18)	1.02 (0.87–1.19)	1.04 (0.88–1.22)
Genital use	636 (27)	755 (33)	1.30 (1.14–1.49)	1.28 (1.12–1.47)
SON[b]				
No powder use	364 (65)	252 (56)	1.00	1.00
Genital use	200 (35)	197 (44)	1.43 (1.11–1.85)	1.35 (1.03–1.76)
USC				
No powder use	494 (63)	435 (56)	1.00	1.00
Non-genital use only	118 (15)	129 (17)	1.25 (0.94–1.66)	1.14 (0.85–1.52)
Genital use	170 (22)	208 (27)	1.39 (1.10–1.77)	1.36 (1.06–1.74)
Pooled[c]				
No powder use	5,815 (59)	4,643 (54)	1.00	1.00
Non-genital use only	1,533 (16)	1,282 (15)	0.98 (0.90–1.07)	0.98 (0.89–1.07)
Genital use	2,511 (25)	2,600 (31)	1.25 (1.16–1.34)	1.24 (1.15–1.33)

[a]Study-specific estimates were determined using unconditional logistic regression and pooled ORs were estimated using conditional logistic regression conditioned on 5-year age groups and study. Multivariate models are adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).

[b]Information on non-genital powder use was not collected in the SON and DOV study.

[c]*P* value for heterogeneity between multivariate study specific ORs equal to 0.61; calculated using Conchran's *Q* statistic test.

NCO, NEC, and USC) or no genital powder use (DOV and SON). We observed no heterogeneity in the risk associated with genital powder use between studies regardless of the reference group ($P = 0.61$; Fig. 1). Results were similar for genital powder users compared with a combined reference group including never users and women whose use of powder was exclusively non genital (covariate adjusted OR, 1.25; 95% CI, 1.16 1.34; data not shown), reflecting the absence of an association between powder use on other parts of the body with ovarian cancer risk (Table 3).

Genital powder use was associated with a similar increased risk of borderline and invasive ovarian cancer overall (Table 4). For borderline tumors, the association was stronger for the serous subtype (OR, 1.46; 95% CI, 1.24 1.72; Table 4) and nonsignificant for the mucinous subtype. For invasive ovarian cancer, we observed small

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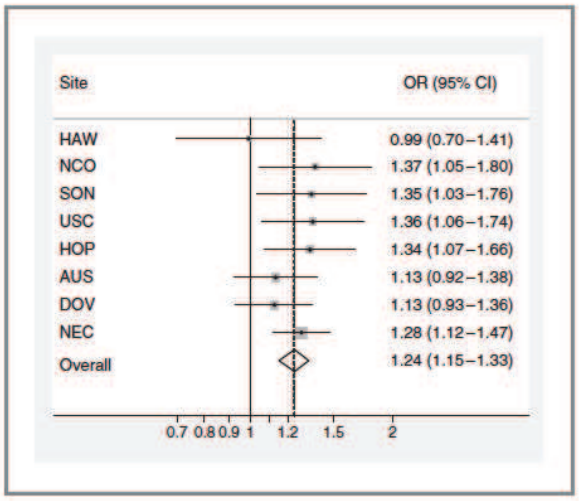

Figure 1. Association between genital powder use and ovarian cancer risk in eight studies, $P_{heterogeneity} = 0.61$. Adjusted for age (continuous), oral contraceptive duration (never use, <2, 2 <5, 5 <10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history, BMI (quartiles), race/ethnicity (non Hispanic White, Hispanic White, Black, Asian, or other) and non genital powder use. Studies listed in decreasing order of effect size SE (funnel plot). No evidence of heterogeneity based on Conchran's Q statistic ($P = 0.61$).

increases in risk of serous (OR, 1.20; 95% CI, 1.09 1.32), endometrioid (OR, 1.22; 95% CI, 1.04 1.43), and clear cell (OR, 1.24; 95% CI, 1.01 1.52) cancer but no significant increase in risk of mucinous cancer (OR, 1.09; 95% CI, 0.84 1.42). Similarly, we observed no significant increase in risk when borderline and invasive mucinous tumors were considered together (data not shown). Risk associated with genital powder use was consistent across studies for bor derline and invasive tumors as well as invasive serous, endometrioid, and clear cell subtypes ($P_{heterogeneity}$ > 0.1; Fig. 2A E), but not for mucinous tumors ($P = 0.08$; Fig. 2F). Genital powder use was associated with increased risk of invasive mucinous tumors in SON, HOP (significantly), and USC (nonsignificantly), whereas in the remaining studies (HAW, NCO, AUS, DOV, and NEC) genital powder use was nonsignificantly associated with reduced risk.

We evaluated cumulative genital powder exposure as a composite variable of frequency and duration of use. We observed similar increased risks of all nonmucinous sub types of epithelial ovarian cancer combined across quartiles of genital powder compared with nonuse: OR_{Q1}, 1.18; 95% CI, 1.02 1.36; OR_{Q2}, 1.22; 95% CI, 1.06 1.41; OR_{Q3}, 1.22; 95% CI, 1.06 1.40; OR_{Q4}, 1.37; 95% CI, 1.19 1.58 (Table 5). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis ($P_{trend} < 0.0001$), no trend in cumulative use was evident in analyses restricted to ever users of genital powder ($P_{trend} = 0.17$; Table 5). Taken together, these observations suggest that the significant trend test largely reflects the comparison of ever regular use with never use. Because tubal ligation or hysterectomy would block the transport of powder through the genital tract to the ovaries, we conducted a sensitivity analysis excluding women who started genital powder use after these procedures. We observed similar associations when

Table 4. Association between powder use and risk of ovarian cancer by behavior and histology

	Model 1[a]			Model 2[a]		
	No powder use	Genital powder use		No genital powder use	Genital powder use	
	n (%)	*n* (%)	OR (95% CI)[b]	*n* (%)	*n* (%)	OR (95% CI)[b]
Controls	5,815 (59)	2,511 (25)		7,348 (75)	2,511 (25)	
All borderline cases	1,035 (58)	504 (28)	1.29 (1.14–1.48)	1,247 (72)	504 (28)	1.30 (1.15–1.47)
Serous	567 (57)	300 (30)	1.46 (1.24–1.72)	700 (70)	300 (30)	1.45 (1.24–1.69)
Mucinous	409 (60)	184 (27)	1.17 (0.96–1.42)	502 (73)	184 (27)	1.19 (0.98–1.43)
All invasive cases	3,470 (54)	2,009 (31)	1.21 (1.12–1.32)	4,471 (69)	2,009 (31)	1.23 (1.14–1.32)
Serous	1,952 (53)	1,197 (32)	1.20 (1.09–1.32)	2,519 (68)	1,197 (32)	1.24 (1.13–1.35)
Mucinous	206 (57)	94 (26)	1.09 (0.84–1.42)	269 (74)	94 (26)	1.06 (0.82–1.36)
Endometrioid	568 (55)	304 (30)	1.22 (1.04–1.43)	723 (70)	304 (30)	1.20 (1.03–1.40)
Clear Cell	327 (54)	187 (31)	1.24 (1.01–1.52)	420 (69)	187 (31)	1.26 (1.04–1.52)

[a]In model 1, the reference group is restricted to women with no powder use except for the DOV and SON studies as these did not collect data on non-genital powder use. The number of cases who reported non-genital powder use was 212 (13%) of all borderline cases, 133 (13%) serous borderline, 93 (14%) mucinous borderline, 1,001 (15%) of all invasive, 567 (15%) serous invasive, 63 (17%) mucinous invasive, 155 (15%) endometrioid invasive, 93 (15%) clear cell invasive. In model 2, the reference group includes all women who did not use genital powders (nonusers and non-genital users combined).

[b]ORs were estimated using conditional logistic regression conditioned on 5-year age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).

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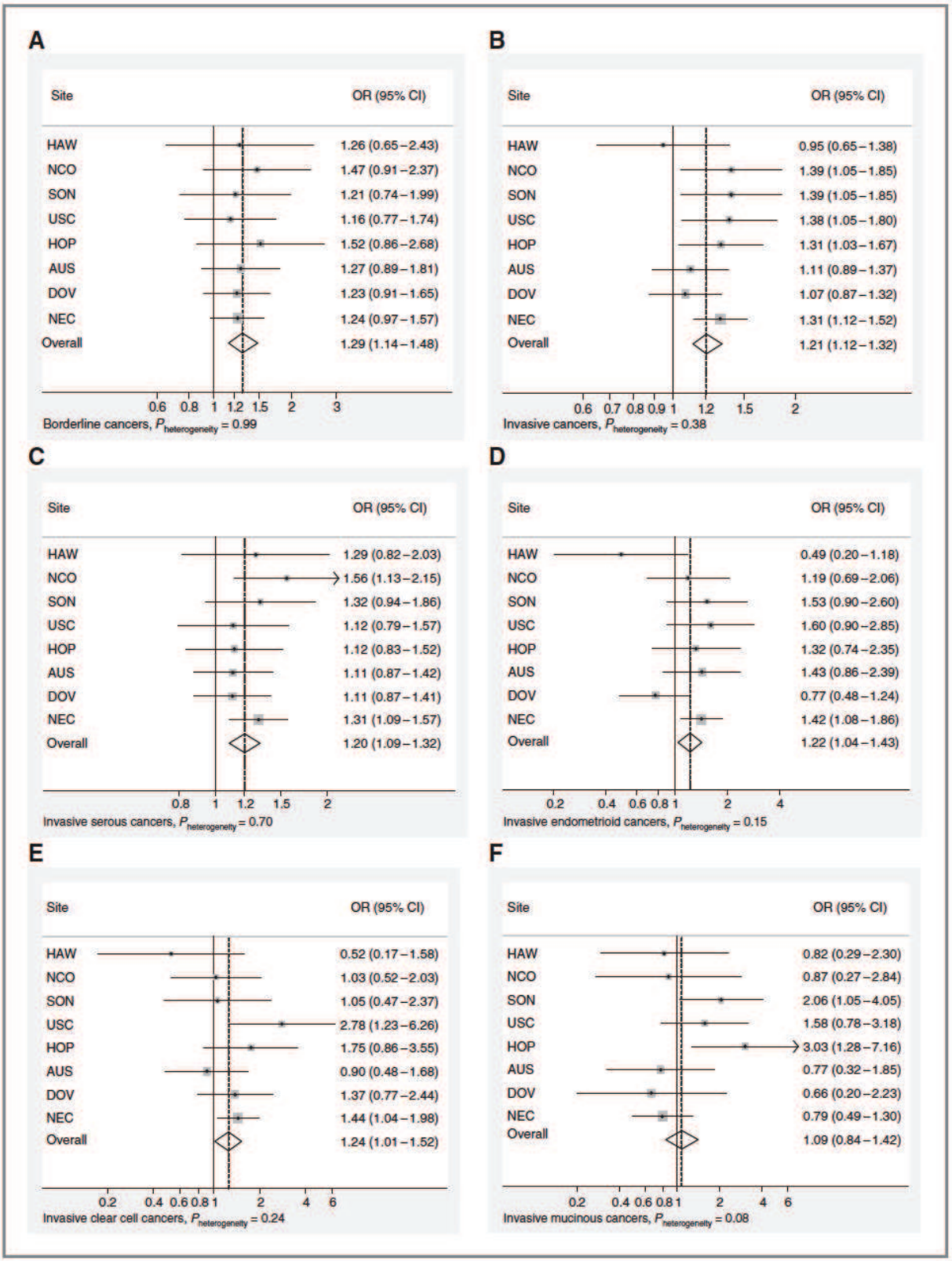

Figure 2. Association between genital powder use and subgroups of ovarian cancer defined by behavior and histology (A. Borderline, B. Invasive, C. Invasive serous, D. Invasive endometrioid, E. Invasive clear cell, F. mucinous.). Estimates are adjusted for the same covariates as in the model presented in Fig. 1.

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Table 5. Association between estimated lifetime applications of genital powder and risk of ovarian cancer (borderline and invasive combined)

Lifetime number of applications[a]		All cases (*N* 7,587)		Nonmucinous cases (*N* 6,361)	
	Controls (%)	Cases (%)	OR[b] (95% CI)	Cases (%)	OR[b] (95% CI)
Never users	6,175 (76)	5,384 (71)	1.00	4,472 (70)	1.00
Quartile 1	509 (6)	534 (7)	1.14 (1.00–1.31)	467 (7)	1.18 (1.02–1.36)
Quartile 2	512 (6)	541 (7)	1.23 (1.08–1.41)	456 (7)	1.22 (1.06–1.41)
Quartile 3	497 (6)	542 (7)	1.22 (1.07–1.40)	457 (7)	1.22 (1.06–1.40)
Quartile 4	486 (6)	586 (8)	1.32 (1.16–1.52)	509 (8)	1.37 (1.19–1.58)
P_{trend}[c]			0.17		0.17

[a]Age-specific 25th, 50th, and 75th percentile cutoff points are 612, 1,872, and 5,400 for participants < 40 years old; 612, 2,160, and 7,200 for 41–50 years; 720, 3,600, and 10,800 for 51–60 years; 1,440, 5,760, and 14,440 for 61–70; 840, 7,200, and 18,000 for > 70 years.
[b]ORs were estimated using conditional logistic regression conditioned on 5-year age groups and adjusted for age (continuous), oral contraceptive duration (never use, <2, 2–<5, 5–<10, or ≥10 years), parity (0, 1, 2, 3, or 4+ children), tubal ligation history (no or yes), BMI (quartiles), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, or other).
[c]Trend excludes never users.

we excluded the 65 cases and 79 controls who started genital powder use for the first time after surgery (OR_{Q1}, 1.19; 95% CI, 1.03 1.38; OR_{Q2}, 1.19; 95% CI, 1.03 1.38; OR_{Q3}, 1.21; 95% CI, 1.04 1.39; OR_{Q4}, 1.36; 95% CI, 1.18 1.57). For studies that collected data on timing of powder use and tubal ligation/hysterectomy, we were able to identify timing of genital powder exposure in relation to surgery based on age of powder use and age at surgery. Restricting our exposure to genital powder applications that occurred before tubal ligation or hysterectomy made no substantive difference in the results.

The association between any genital powder use and ovarian cancer risk was stronger among women with BMI < 30 kg/m^2 (OR, 1.28; 95% CI, 1.17 1.39) than for women with BMI ≥ 30 (OR, 1.14; 95% CI, 0.98 1.32; $P_{interaction}$ = 0.01). We observed no significant interactions between genital powder use and parity, reported history of endo metriosis, tubal ligation/hysterectomy, or menopausal sta tus (all $P_{interaction}$ > 0.1). The association between genital powder use and ovarian cancer risk was similar for women who started use between 1952 and 1961 (OR, 1.36; 95% CI, 1.19 1.56), between 1962 and 1972 (OR, 1.27; 95% CI, 1.11 1.46), and after 1972 (OR, 1.31; 95% CI, 1.15 1.51). However, we observed an attenuated association for women who started genital powder use before 1952 (OR, 1.08; 95% CI, 0.93 1.25).

Discussion

This pooled analysis of eight case control studies sug gests that genital powder use is associated with a modest 20% to 30% increase in risk of developing epithelial ovarian cancer, including serous, endometrioid, and clear cell tumors, but is less relevant to invasive mucinous tumors. Our findings are consistent with and extend the findings of three meta analyses that have reported an increased risk of epithelial ovarian cancer with genital powder use (1, 4, 5) by including dose response and histology specific analyses. Our estimate of the overall association between genital powder use and ovarian cancer risk was slightly attenuated compared with previous estimates from meta analyses. Possible reasons for the difference include the lack of restriction to published results, data harmonization between studies that allowed similar definitions for the exposure and covariates, and chance. On the basis of the consistency in the epidemiologic literature on talc based powder and ovarian cancer risk, the International Agency for Research on Cancer (IARC) classified talc based body powder as a class 2b carcinogen "possibly carcinogenic to human beings" (29).

The biologic plausibility for the observed association between genital powder use and ovarian cancer risk has been challenged because evidence for dose response has been inconsistent (2, 4, 5, 9, 10, 15, 22). The lack of significant dose response may reflect the difficulty inher ent in accurate recollection of specific details of frequency and duration of genital powder use. Also, because not all powder products contain talc, various products may differ in their potential carcinogenic effects. Alternatively, the association between genital powder exposure and ovarian cancer risk may not be linear and a modest exposure may be sufficient to increase cancer risk. Talc containing pow ders are hypothesized to promote cancer development by ascending the female genital tract and interacting directly with the ovarian surface epithelium, leading to local inflammation characterized by increased rates of cell division, DNA repair, oxidative stress, and elevated inflammatory cytokines (13). Particles in solution easily ascend the genital tract (30, 31). Our finding of slightly attenuated associations following exclusion of women with powder exposure after tubal ligation or hysterectomy are not supportive of this hypothesis, but risk estimates in this subgroup analysis may have randomly differed from those including all women because of the reduction in

sample size. Talc particles have been observed in the ovaries of humans (32) and in rodent models (33, 34), but little is known about the biologic effects of genital powder use.

In the current analyses of the various histologic sub types of ovarian cancer, we confirmed previous reports of increased risk of serous invasive tumors with genital powder use (2, 4, 8, 9, 22). We also observed significantly increased risk of both endometrioid and clear cell inva sive ovarian tumors with use of genital powder, and this finding was consistent across studies. It has been sug gested that both endometrioid and clear cell ovarian tumors may originate from ectopic uterine endometrium (endometriosis) implanted on the ovary (17). In contrast, we observed no significant associations between genital powder use and either borderline or invasive mucinous ovarian cancer. The lack of a significant association for mucinous tumors may be due to the relatively small number of these tumors or could be an indication that powder exposure is not relevant to the pathogenesis of this histologic type. Studies have noted that ovarian cancer risk factors and molecular characteristics differ for mucinous tumors (16 18, 23, 35 39).

Limitations of our pooled analysis include differences in the wording of questions about genital powder use between studies and the retrospective nature of the exposure ascer tainment. Women who were classified as genital powder users varied from "ever" use (AUS) or "ever regular" use (SON) to powder use for at least 6 months (HAW, HOP, NCO, NEC, and USC) or at least 1 year (DOV). Differences in genital powder questions result in varying levels of misclassification of true genital powder exposure. However, because exposure definitions are the same for cases and controls within each study, misclassification of genital powder exposure due to the question wording would be nondifferential, leading to an underestimation of the true association for any given study. These studies were retro spective in nature and therefore potentially susceptible to bias if cases were more likely to report genital powder use than controls. Although nongenital powder use was not associated with ovarian cancer risk, it is nevertheless pos sible that any over reporting of powder use by cases might have been limited to reporting of genital powder. Our analyses were also limited by missing data on genital powder use; however, missingness was not associated with the distribution of any of the ovarian cancer risk factors examined and was thus not likely to bias our results. Strengths of our analysis include a large sample size and pooled analysis of individual data, allowing evaluation of the association of genital powder use with less common histologic subgroups of ovarian cancer, careful harmoniza tion of the data based on comparison of study question naires, the use of a composite variable combining duration, and frequency to assess dose response relationships.

In conclusion, our large pooled analysis of case con trol studies shows a small to moderate (20% 30%) increased risk of ovarian cancer with genital powder use, most clearly pertaining to nonmucinous epithelial ovar ian tumors. More work is needed to understand how genital powders may exert a carcinogenic effect, and which constituents (e.g., talc) may be involved. Because there are few modifiable risk factors for ovarian cancer, avoidance of genital powders may be a possible strategy to reduce ovarian cancer incidence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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